Home Office

NON-TECHNICAL SUMMARY

The structure and function of neural circuits underlying information processing in the mammalian brain

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Sensory physiology, neuroscience, brain, information processing, neurons

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

Understanding how the brain processes information is one of the greatest scientific challenges. On top of that, we have started to realize that many devastating diseases such as autism spectrum disorder or schizophrenia are essentially due to erroneous information processing in the neural networks of the brain.

The aim of this project is to contribute to our understanding of information processing in the brain by studying how sensory information (smells, sounds, images etc) are processed in the rodent brain. We aim to address questions such as how does the state of the animal (whether it has learned something, whether it is interested in a smell) influence how neurons respond, how information is processed. We will investigate the architecture of the neuron network (i.e. which neurons are connected to others), how the activity of a neuron or the response to a smell is shaped by its connections. Furthermore, we will address how learning itself influences the activity of neurons and possibly the connections between neurons.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

While understanding functional connectivity of neural networks is a key scientific challenge in its own right, a growing number of cognitive disorders are linked to alterations in neuronal connectivity. This includes diseases as socially and economically devastating as autism spectrum disorders or schizophrenia that together are estimated to affect more than 1 in 100 people.
Our work will not directly address these diseases. We will, however, provide essential understanding about how networks of neurons process information, and aim to find out basic principles. This will allow us and others at a later stage to find out how exactly this information processing is perturbed in the diseased brain.
Furthermore, the techniques we will develop in order to improve the way we record activity from the brain will help the development of “brain-computer-interfaces / neural prosthetics”: crucial clinical tools to aid people who have e.g. lost a limb or sight or hearing. We are actively collaborating with companies in this sector and protect intellectual property developed in order to allow its efficient translation.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

We will exclusively use mice and few rats. We will use approximately 14,000 mice and 100 rats over a five year research program.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

We will perform behavioural experiments where animals will be observed e.g. moving in an open space, investigating odours etc. We will perform terminal experiments under general anaesthesia where – except for the induction of anaesthesia typically through an inhalant – the animal will feel no pain but we will be able to obtain highly valuable information about circuit architecture. We will perform behavioural experiments where the animals are motivated to e.g. discriminate between similar stimuli by a small reward (sugar water). Here, it is often necessary to increase motivation by withholding water or food for a period of up to 24 hours but animals are not expected to experience more than mild or rarely moderate levels of discomfort (as animals display normal grooming, exploratory etc behaviour). Some animals will require surgical procedure (under general anaesthesia) to allow subsequent electrical recording from brain cells in the awake animal. Here, care is taken to use the highest surgical standards (similar to human surgeries) and minimize discomfort through use of analgesics. These are key experiments as they allow recording from the brain “as is” and help to understand a complete picture of information flow in the brain, unperturbed by anaesthesia.

Thus, adverse effects are expected to be generally mild and only rarely moderate – genetic or pharmacological modifications will generally be only applied to a tiny region or very small number of cells in the brain; surgical procedures are well established and generally minimally invasive. A social and enriched environment will be provided wherever possible to minimise social stress.

At the end of the experiment animals will be killed humanely and analysed ex vivo.

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

Understanding of information processing in the brain (healthy or diseased) is still in its infancy. Thus, as computer simulations need validated input to generate meaningful output, we cannot yet replace the direct observation of nature by simulations.

As we aim to contribute to the understanding of the human brain on disease and the computations underlying behaviour we have to focus on a species that is both phylogenetically close to humans and genetically tractable. Thus, we have to focus on rodents, and especially mice that allow targeted genetic manipulations to create models of disease.

Reduction

Explain how you will assure the use of minimum numbers of animals.

We have established highly quantitative physiological, behavioural, and anatomical assays. This, together with our strong statistical background will ensure that we can determine and use the minimal number of animals that will generate meaningful, reproducible, valid results. As we have in the past, we

will use extensive computational approaches to focus our experimental efforts and thus further reduce animal numbers. Finally, wherever possible we will use within animal comparisons to assess treatment consequences which will allow us to use paired and much more powerful statistical tools and thus further reduce animal need.

Furthermore, in the last years we have established group-housing of animals that allows to continuously perform behavioural analysis over periods of up to 18 months. This in turn allows to collect highly quantitative and extensive data on a much smaller number of animals as previously possible. We have developed large-scale electrophysiological recording techniques that allow us to obtain the same amount of information with again substantially smaller numbers of animals. Finally, large-scale anatomical investigations have the potential to replace anatomical mapping efforts in many hundreds of animals with extensive analysis of 2-3 animals.

This together has already allowed us to substantially reduce the numbers of animals employed in our research over the last years and with further experimental advance will continue to help reduction.

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

We have worked hard to establish a set of natural behavioural paradigms where mice are group housed in enriched environments and left unperturbed by human interference. This not only ensures highest quality (reproducible) data but also minimises animal stress and substantially increases animal welfare.

More generally, as we aim to contribute to the understanding of the human brain on disease and the computations underlying behaviour we have to focus on a species that is both phylogenetically close to humans and genetically tractable. Thus, we focus on rodents, and especially mice that allow targeted genetic manipulations to create models of disease.